Novel epigenetic control found for critical brain proteins in memory strengthening

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Farah Lubin. Credit: UAB

Understanding how memories form and are retrieved has applications to psychiatric, neurological and neurodegenerative disorders, and may be helpful to attenuate maladaptive memories in psychiatric disorders.

Two broad findings have been seen in memory reconsolidation, which is the retrieval and strengthening of a recent memory. The first broad finding is that, during memory reconsolidation, changes in translational control—the process of forming new proteins from activated genes—occur in areas of the brain related to memory formation. The second broad finding is that epigenetic mechanisms—various molecular modifications known to alter the activity of genes without changing their DNA sequence—are also somehow actively involved during memory reconsolidation or strengthening.

Now, researchers at the University of Alabama at Birmingham have described a novel mechanism that links epigenetic change to translational control. In the *Journal of Neuroscience*, they report how several particular epigenetic changes in the hippocampus of the rat brain control downstream regulation of translation in brain neurons during fear memory reconsolidation, acting through a gene called Pten. The downstream target affected by changes in PTEN enzyme levels is the AKT-mTOR pathway, one of the main translation control pathways involved in memory reconsolidation. PTEN was already known to be a potent inhibitor of AKT-mTOR, but was not previously linked to epigenetic control of memory.

"These findings could be critical in treatment of memory disorders, such as post-traumatic stress disorder," said Farah D. Lubin, Ph.D., associate professor in the UAB Department of Neurobiology. "PTSD is thought to be caused by the lack of extinction of a fear memory. Altering this memory during the reconsolidation process could help in re-associating the memory with a less traumatic context."

Memory consolidation is the process that stabilizes a memory after it is first acquired in the brain. Memory reconsolidation occurs when that memory is retrieved, and the memory may be modified or strengthened.

In the study led by Lubin, researchers found that retrieval of a contextual fear memory in rats briefly increased levels of the enzyme EZH2, an enzyme known to add methyl groups to histones. Histones are proteins that help package and order DNA in the chromosome, and they also play a role in epigenetic gene regulation. Along with the increased EZH2, the researchers found increased methylation of histone H3, specifically the addition of three methyl groups to the lysine 27 amino acid of histone H3. That trimethylation of the histone by EZH2, known as H3K27me3, correlated with decreased levels of PTEN enzyme.

Examination of the DNA encoding for the Pten gene showed increased levels of H3K27me3 bound to the DNA, as well as DNA methylation, across the promoter and coding regions of the Pten gene. DNA methylation is another form of epigenetic control, and both the histone epigenetic change and the DNA epigenetic change indicated transcriptional silencing of the Pten gene.

The UAB researchers next used small interfering RNA, or siRNA, to knock down genes. Through knockdown experiments, they showed that levels of H3K27me3 and PTEN appear to directly control the AKT-mTOR pathway.

Knockdown of the gene for the H3K27me3 methyltransferase enzyme, Ezh2, in the hippocampus, which is the memory consolidating region of the brain, prevented decreases of PTEN and activation of AKT-mTOR during memory reconsolidation. But when the Ezh2 and Pten genes were knocked down at the same time, the AKT-mTOR pathway was activated.

"In the present study, we found that H3K27me3 regulated Pten repression necessary for mTOR phosphorylation during memory reconsolidation," Lubin said. "As a result, we have identified a novel epigenetic pathway critical for regulation of translational control mechanisms during memory reconsolidation."

Co-authors with Lubin of the paper, "EZH2 methyltransferase activity controls Pten expression and mTOR signaling during fear memory reconsolidation," are Timothy J. Jarome, Gabriella A. Perez, Rebecca M. Hauser and Katrina M. Hatch, UAB Department of Neurobiology.

More information: Timothy J. Jarome et al, EZH2 Methyltransferase Activity Controls Pten Expression and mTOR Signaling during Fear Memory Reconsolidation, *The Journal of Neuroscience* (2018). DOI: 10.1523/JNEUROSCI.0538-18.2018

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